ACUTE TOXICITY SUMMARY

EPICHLOROHYDRIN

(1-chloro-2,3-epoxy-propane)

CAS Registry Number: **106-89-8**

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**1,300 μg/m³**
Critical effect(s)	eye and nasal irritation in human volunteers
Hazard Index target(s)	Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994)

Description	colorless liquid
Molecular formula	C_3H_5ClO
Molecular weight	92.5
Density	1.181 g/cm^3 @ 20°C
Boiling point	117.9°C
Melting point	-25.6°C
Vapor pressure	13 mm Hg @ 20°C
Flash point	33.9°C
Explosive limits	3.3% - 14.5 % by volume in air
Solubility	slightly soluble in water, soluble in most organic solvents
Odor threshold	0.93 ppm (chloroform-like, irritating odor)
Metabolites	N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine
Conversion factor	1 ppm = 4 mg/m³

III. Major Uses or Sources

Epichlorohydrin is a major raw material used in the manufacture of epoxy and phenoxy resins. It is also used as a solvent and in the synthesis of glycerol. Other uses include that of insect fumigation and as a chemical intermediate for the formation of glycidyl acrylate derivatives such as those used in the formation of eyeglass lenses (HSDB, 1994).

IV. Acute Toxicity to Humans

Case reports of exposure to epichlorohydrin in the workplace, either through inhalation or dermal contact, describe symptoms including burning sensations of the nose and throat, chest congestion, running nose, eye tenderness, and headache followed by nausea, in addition to reddening and burning sensations of the exposed skin, which persist for several days to 2 months (Wexler, 1971, as cited in NIOSH, 1976). Epichlorohydrin is a strong skin sensitizer following dermal contact

(U.S.EPA, 1984). Epichlorohydrin is a reactive epoxide and a known mutagen. In vitro exposure of human lymphocytes to 10^{-11} to 10^{-4} M epichlorohydrin resulted in dose-dependent chromatid and chromosomal breaks (HSDB, 1994).

Predisposing Conditions for Epichlorohydrin Toxicity

Medical: Asthmatics may be more sensitive to the irritant effects of inhaled epichlorohydrin.

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

A six-hour exposure to epichlorohydrin with a 14-day follow-up showed the median lethal concentration to be 360 ppm (1,440 mg/m³) in rats (Laskin *et al*., 1980). An LC_{50} of 445 ppm (1,780 mg/m³) for four hours was reported for rabbits (HSDB, 1994). An eight-hour exposure to 250 ppm (1,000 mg/m³) killed two-thirds of the rats exposed (sample size not given) (LeFaux, 1968). A single subcutaneous injection of 75 mg/kg resulted in swelling of proximal renal tubular epithelium in male rats (Kluwe *et al*., 1983).

Deaths occurred in rats exposed chronically to a concentration of 68 ppm (272 mg/m³) epichlorohydrin for an unknown duration (IRIS, 1994). Tumors induced by chronic epichlorohydrin exposure are typically local to the area of initial exposure (U.S.EPA, 1984). Nasal carcinomas are among the tumors known to occur following epichlorohydrin exposure (U.S.EPA, 1984).

VI. Reproductive or Developmental Toxicity

Fetotoxicity and toxicity to dams were reported in mice exposed to 120 mg/kg/day epichlorohydrin via gavage during days 6-15 of gestation; however, no teratogenic effects were noted (Marks *et al*., 1982). Teratology studies in rats and rabbits yielded negative results for embryotoxicity and teratogenicity (John *et al*., 1983a).

Maternal toxicity, as measured by a decrease in body weight and food consumption, was demonstrated in pregnant rats following exposure to 25 ppm (100 mg/m³) epichlorohydrin for 7 hours/day on days 6-18 of gestation (John *et al*., 1983a). Additionally, exposure of male rats to 25 ppm for 5 days/week for 10 weeks resulted in a transient loss in fertility (John *et al*., 1983b).

Injury to epididymal tissue, testicular atrophy, and increases in the number of sperm with abnormal morphology have been observed in male rats exposed via single subcutaneous injection to 75 mg/kg epichlorohydrin (Kluwe *et al*., 1983). Although animal studies indicate that male fertility is affected by exposure to high doses of epichlorohydrin, a human epidemiologic study showed no changes in male fertility rates among workers (HSDB, 1994).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 0.33 ppm (1,300 μg/m³)

Study	Wexler (1971) as cited in NIOSH, 1976
Study population	occupationally exposed workers
Exposure method	during work-shifts (occupation not given)
Critical effects	irritation of eyes and nasal passages
LOAEL	20 ppm
NOAEL	not reported
Exposure duration	1 hour
Extrapolated 1 hour concentration	20 ppm
LOAEL uncertainty factor	6 (mild irritation)
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	0.33 ppm (1.3 mg/m³, 1,300 μg/m³)

The Wexler (1971) study represents the only human data but it was not available for review. The report by NIOSH (1976), which reviewed the Wexler study, was therefore used as the basis for the REL.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Exposure of 8 rats for 6 hours/day, 5 days/week for 19 days to 17 ppm epichlorohydrin resulted in no pulmonary histopathological abnormalities as compared to controls (Gage, 1959). The ERPG documentation for epichlorohydrin (AIHA, 1992) erroneously refers to Laskin *et al*. (1980) as a teratology study instead of a carcinogenicity study. In addition, the extrapolation of sub-chronic animal exposures in the Gage study to acute human exposures involves considerable uncertainty that is not accounted for in the ERPG document. The ERPG-2 value of 20 ppm (76 mg/m³) is therefore poorly substantiated.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

Subacute exposures of rats and mice (5/sex) to 100 ppm epichlorohydrin 6 hours/day, 5 days/week, 9 exposures in 12 days, resulted in focal pneumonitis and inflammation and degeneration of nasal epithelium in addition to decreased weight gain (Quast *et al*., 1979a, b). Kidney toxicity was seen in the rats exposed to 100 ppm. No lethality was observed. It was concluded that acute exposure to 100 ppm would not cause fatality in humans. Thus AIHA

(1992) selected 100 ppm (380 mg/m³) as the ERPG-3 for epichlorohydrin. This value can be considered a subchronic NOAEL for lethality in mice, but the lack of uncertainty factors for the extrapolation of animal to human exposures, in addition to those required for consideration of sensitive individuals, dictate that this value should be reevaluated. The small sample sizes in the rodent studies, and the absence of peer-reviewed data used to derive the NOAEL, further weaken the scientific validity of this value. The ERPG-3 value is based on severe, non-lethal effects and not on lethality data. An inhalation LC_{50} in mice of 2,998 mg/m³ for 2 hours is reported by the World Health Organization (1992).

VIII. References

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